REMARKS/ARGUMENTS

Claims 1, 2, 4-8, 13, 15, 16, 20-22, 27-30, 35-38, 43 and 45 are pending in the application. Claims 1, 21 and 22 are allowed. Claims 2, 4-8, 13, 15, 16, 20, 27-30, 35-38, 43, and 45 are rejected. Claim 15 has been cancelled without prejudice or disclaimer. Claims 46-48 are newly presented. Applicants wish to thank the Examiner for the allowable subject matter and respectfully request reconsideration for the allowance of the remaining pending claims in view of the following remarks.

In order to provide a varying scope of invention, claims 46-48 have been added. These claims are fully supported in the specification, claims and drawings as filed; no new matter has been added. Support for the use of a vector can found in the Specification, e.g., at page 18, line 17, to page 19, line 8 as well as the claims as filed. Support for treatment of a neurodegenerative disease associated with amyloid pathology can be found in the Specification e.g., at page 3, lines 5-10; page 7, lines 10-15; page 11, lines 2-17 and Figures 5, 10, 11, 12C, 12D, 22-24. Support for treatment of a neurodegenerative disease associated with a mutation of an amyloid precursor protein, presenilin-1 or presenilin-2 can be found in the Specification, e.g., at page 2, lines 26-36; page 3, lines 9-12; page 11, lines 2-17 and Figures 5, 10, 11, 12C, 12D and 22-24.

Applicants also wish to thank the Examiner for her time and consideration during the courteous interview of December 7, 2005. Applicants undersigned representative discussed proposed amendments for overcoming the rejections in the previous office actions. During the interview, the Examiner indicated that the proposed amendments would over come rejection from sections 7 and 12 of the previous office actions.

ENABLEMENT REJECTIONS UNDER 35 U.S.C. § 112, 1ST ¶ 0F CLAIMS 2, 4-8 13, AND 15-16,

Claim 2, 4-8, 13, 15 and 16 stand rejected under 35 U.S.C. 112, first paragraph, because allegedly the Specification, while being enabling for a polypeptide that suppresses

neuronal death associated with Alzheimer's disease having amino acid sequence of SEQ ID NO: 5 to [..] 60, wherein one amino acid has been substituted, deleted, inserted and/or added, does not reasonably provide enablement for the full scope of a polypeptide as claimed in section b) essentially for reasons of record in section 8 of the office action of March 16, 2004 and in section 11 the office action of April 13, 2005.

Claims 15 and 16 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement for reasons of record in section 10 the office action of March 16, 2004 and in section 13 the office action of April 13, 2005.

These rejections are respectively traversed and Applicants will address each in turn. In regard to first part of the rejection, contrary to the Examiner's assertions, the Specification provides extensive teaching on how to make and use the claimed polypeptides that suppress neuronal death associated with Alzheimer's disease including those in which multiple amino acids have been substituted, deleted and/or inserted. See the Specification e.g., at page 12, lines 10-21; page 12, lines 22 to page 13, line 8; and Applicants' remarks from the response of 10/12/05 at page 10-11.

However, in order to expedite prosecution of the application and without acquiescing to the propriety of the Examiner's rejection, Applicants have amended claims 2, 5 and 6 to now recite "one amino acid has been substituted, deleted, inserted, or added." As the Examiner correctly points out on page 4 of the instant office action, the Specification provides specific teaching for this limitation. Accordingly, withdrawal of the rejection is respectfully requested.

In regard to the rejections of claims 15 and 16, Applicants traverse for reasons of record from the response of 10/12/05. Additionally, Applicants respectfully disagree with the Examiner's contention that Alzheimer's disease in particular..[is] not limited to amyloid pathology" (11/04/05 Office Action at page 5, emphasis added). The Examiner would appear to be inferring the claims are not enabled for treatment of Alzheimer's disease beyond amyloid pathology . Such is not the case.

The claimed compositions are suitable to treat not only pathological conditions associated with amyloid pathology, but also Alzheimer's disease (AD) in general. This is evidenced not only by the Specification, but also by a significant body of peer reviewed scientific research. For example, Hardy *et al.* describe that *"autosomal-dominant Alzheimer's disease can be caused by mutations in the APP, presenilin 1 (PS1), or presenilin 2 (PS2) gene"* (Hardy et al., Science, 282, 1075-1079, 1077, 1998). Also, the Specification demonstrates that various embodiments of the claimed polypeptides can suppress neurotoxicities caused by not only an amyloid peptide, but also mutants of APP, PS-1 and PS-2. For example, Figure 12 of the Specification shows that the claimed polypeptides and also the vector encoding them, can suppress neurotoxicities caused by K595N/M596L APP (NL-APP), V642I APP, M146L PS-1 and N141I PS-2 mutants as well as neurotoxicity of Aβ43 (See the Specification at Figs. 12 and 15).

Other researches have demonstrated that the claimed polypeptides also inhibit neurotoxicities caused by a number of other familial AD-related mutations such as A617G-APP, L648P-APP, A246E-PS1, L286V-PS1, C410Y-PS1 and H163R-PS1, APP stimulation with anti-APP antibody, and other Aβ peptides such as Aβ1-42 and Aβ25-35 (See Abstract of Hashimoto et al., J. Neurosci. 21: 9235-9245, 2001). Hashimoto et al. have shown that the claimed polypeptides have *"the high potency, full efficacy, and strict selectivity of the action against a very wide spectrum of AD insults"* (Id. at 9244, left column, lines 20-22, emphasis added). These actions are in stark contrast with those of known neurotrophic factors such as ADNF, IGF-I, bFGF. While these latter factors can suppress neurotoxicity of Aβ, they exhibit *"incomplete or little effect"* on neurotoxicities caused by NL-APP, M146L PS-1 and N141I PS-2 (See Niikura et al., J. Neurosci. Res. 70: 380-391, 384 (right column), 2002).

Researchers have also indicated that the neurotoxicities of APP, PS1 and PS2 mutants are likely mediated by mechanisms which are, at least in part, distinct from those of Aβ peptides. For example, Niikura et al. describe that familial AD mutant APPs can exert cytotoxicity independently of Aβ (page 384, left column, lines 16-18). Niikura et al. further

describe that the cytoplasmic domain 20 of APP (i.e. His^{657} to Lys^{676}), not the Aβ42 region, is implicated in the cytotoxic function of antibody-stimulated APP (Id. at page 384, lines 22-24).

It is also noteworthy that even when NL-APP is modified so as **not** to produce Aβ42 peptide, the modified NL-APP (NL-APPΔ41/42) still exerts neurotoxicity in an Aβ42 independent manner. Moreover, the claimed polypeptides have been shown to suppress this form of neurotoxicity as well. (See Hashimoto et al., BBRC 283: 460-468, 466 (left column), 2001). It has been also shown that PS-1 and PS-2 mutants exert neurotoxicities through their own mechanisms (See Hashimoto et al., J. Neurochem. 80: 426-437, 2002; See Also Hashimoto et al., J. Pharmacol. Exp. Therapeutics 300: 736-745, 2002), and that the claimed polypeptide, as well as a vector that encodes them, can suppress the neurotoxicities of these PS-1 and PS-2 mutants (See e.g., Fig. 12 of the instant Specification).

Accordingly, given that the mutant genes associated with Alzheimer's disease have neurotoxic mechanisms distinct from that of Aβ, and that embodiments of the claimed polypeptide and vectors encoding them can suppress the neurotoxicities of these mutants as well as those of Aβ peptides, Applicants respectfully submit that the therapeutic target of the claimed polypeptides is not be limited to amyloid pathology, but extends to multiple aspects of Alzheimer's disease so as to be a treatment for Alzheimer' disease in general.

In order to expedite prosecution of the application and without acquiescing to the propriety of the Examiner's rejection, Applicants have cancelled claim 15 and have amended claim 16 to now recite "an amount of the polypeptide effective to treat Alzheimer's disease." Support for this amendment is found in the Specification and the discussions above. Accordingly, withdrawal of the rejection is respectfully requested.

ENABLEMENT REJECTIONS UNDER 35 U.S.C. § 112, 2ND ¶ 0F CLAIMS 2, 4, 5-8, 13, 15-16, 20, 27-30, 35-38, 43 AND 45,

Claims 2, 4, 5-8, 13, 15-16, 20, 27-30, 35-38, 43 and 45 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for allegedly failing to particularly

point out and distinctly claim the subject matter which applicant regards as the invention. These rejections are respectively traversed and Applicants will address each in turn.

Claims 2, 5, and 6 stand rejected as allegedly vague and indefinite in section b), which recites a polypeptide defined by amino acid sequence (SEQ ID NOs: 5 to 60), wherein such polypeptide contains amino acid substitutions, deletions, insertions and additions, which makes the structure of the claimed molecular embodiments mutually exclusive.

Applicants traverse this rejection. However in order to expedite prosecution of the application and without acquiescing to the propriety of the Examiner's rejection, Applicants have amended claims 2, 5 and 6 to now recite that "one amino acid has been substituted, deleted, inserted, **or** added." as well adopting the language suggested by the Examiner on page 7 of the instant office action. Accordingly withdrawal of the rejection is respectfully requested.

Claim 5, as amended, stands rejected as allegedly being indefinite for recitation of "a mutant sequence of SEQ ID NO: 4". Applicants respectfully traverse this rejection, the claim is definite. However without acquiescing to the propriety of the rejection, Applicants have amended the claim to obviate the rejection. Claim 5 now recites the limitation of "wherein the DNA does not comprise the sequence of SEQ ID NO:4" Applicants respectfully point out the where the Specification positively recites elements of a claim, the claims may be properly amended by subtracting those elements. The MPEP, the CCPA, and the Federal Circuit **are all absolutely unequivocal on this point**:

> If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See In re Johnson, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also Ex parte Grasselli, 231 USPQ 393 (Bd. App. 1983), aff'd mem., 738 F.2d 453 (Fed. Cir. 1984).

SEQ ID NO:4 is explicitly recited throughout the Specification (See e.g., the Specification at page 7, lines 10-15; page 16, lines 13-30; and the sequence listing). Accordingly, per the direction given by the MPEP, CCPA and Federal Circuit, Applicants

respectfully submit that the amendment to claim 5 is fully supported in the Specification and claims as filed.

Claims 20, 28 and 36 stand rejected as allegedly being vague and ambiguous for recitation "amino acid sequence consisting of 3 to 5 arbitrary amino acids (SEQ ID NO: 100)". Applicant respectfully traverse this rejection. However in order to expedite prosecution of the application and without acquiescing to the propriety of the Examiner's rejection, Applicants have amended the claims to 20, 28 and 36 overcome the rejection. Accordingly, withdrawal of the rejection is respectfully requested.

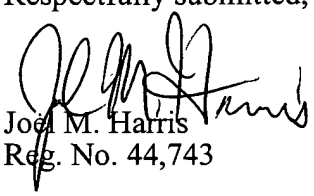
Claims 4, 7-8, 13, 15-16, 27, 29-30, 35, 37-38, 43 and 45 stand rejected as allegedly being indefinite for being dependent from alleged indefinite claims. Applicants respectfully submit that these rejections have been obviated by the arguments and amendments described above.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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Attachments:

1) Hashimoto et al. et al., J. Neurosci.
2) Hashimoto et al., J. Neurochem.
3) Hashimoto et al., J. Pharmacol.
4) Hashimoto et al., BBRC
5) Niikura et al., J. Neurosci. Res.

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